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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/650,591	08/27/2003	Noubar B. Afeyan	COTH-P02-001	7918

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EXAMINER	
MEAH, MOHAMMAD Y	
ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/650,591	AFEYAN ET AL.	
	Examiner	Art Unit	
	MD. YOUNUS MEAH	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,14-34 and 37-41* is/are pending in the application.

4a) Of the above claim(s) *3,28 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-5, 14-27 and 30-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 3-5,14-34 and 37-41 are pending. With supplemental amendment of this application, the applicants, on 05/7/ 2008, argue on the rejection of claims 1, 4-5, 14-27 and 30-41. Claims 3, 28-29 remain withdrawn. Previous final rejection of date 01/23/2008 is treated as non-final office action as stated on mutual agreement during Telephone interview of February 1 2008.

Specification Objection

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code at paragraphs 034 and 0579. See MPEP § 608.01.

Sequence compliance

Applicant is required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the claims and/or specification. It is particularly noted that variety of sequences are recited in the specification without giving any sequence listing. Appropriate correction is required. See particularly 37 CFR 1.821(d).

Claim Rejections

35 U.S.C 112 Enablement requirement

Rejection of claims 38-40 under 35USC enablement requirement is withdrawn after finding applicants argument reasonable.

CLAIM Rejection - 35 U.S.C 102

As explained in prior actions claims 1, 4, 14, 19, 21-27, 30, 33, 34 and 37 are rejected under 35 U.S.C.102(b) as being anticipated by Davis et al. (WO 00/64485).

Davis et al. teach fusion proteins wherein enzymes (serine protease, chymotrypsin, metalloproteinase, etc) which catalyze degradation of a specific target are conjugated to binding partners wherein the binding partner is a ligand binding domain or protein or peptide or antibody (i.e, immunoglobulin, Fab, $F(ab)_2$ see parg. 0064-0065) to the target with or without a linker and resulting fusion protein has greater (catalytic or more than one) activity than the unconjugated molecule. The chimeric protein of Davis et al. bind to the target and antagonize/inhibit/degrade a wide variety of receptors and/or intermediary signaling molecules such as cytokines, EGF-like factors, etc. Davis et al. use the fusion protein as a pharmaceutical composition wherein the targeted enzyme is protease (trypsin, chymotrypsin) and use the pharmaceutical composition for treating autoimmune disease, infectious diseases , cancer, etc.

Applicants argument that Davis et al do not teach a fusion protein is not found persuasive because, like applicants, Davis et al. conjugate a catalytic domain (i.e., protease) to a targeting moiety (a protein, claim 126 of Davis et al) via with/or without chemical cross linking agent. Davis called it chimeric protein which is fusion of two

polypeptides (a fusion protein). Applicants' argument that a fusion protein is a protein conjugate created by only joining two genes together is contradictory to what applicants specification teaches. The specification teaches (paragraph 0009) that a fusion protein may be generated in a variety of ways, including chemical coupling (Davis et al make chimeric protein by this method) and cotranslation. Prior art (see last paragraph of column one of page 571 of Bhatia et al Intl. J. Cancer 2000, 85, 571-577) also defines a fusion protein as a protein conjugate that is made either by chemical coupling or recombinant DNA methodology.

CLAIM Rejection - 35 U.S.C 103a

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 14, 18 19-21, 22-27, 30, 33--34, 37-38 are rejected under 35 U.S.C. 103(a) by Davis et al. (WO 00/64485) in view of, Bhatia et al (Intl. J. Cancer 2000, 85, 571-57) and Whitcomb et al. (US PAT 6406846).

Davis et al. teach fusion proteins wherein enzymes (serine protease, chymotrypsin, etc) which catalyze degradation of a specific target are conjugated to binding partners wherein the binding partner is ligand binding domain or protein or peptide or an antibody (immunoglobulin, Fab, $F(ab)_2$ see parg. 0064-0065)) **to the**

target with or without a linker and resulting conjugate has greater (catalytic or more than one) activity than the unconjugated molecule. The chimeric protein of Davis et al. bind to the target and antagonize/inhibit /degrade a wide variety of receptors and/or intermediary signaling molecules such as cytokines, EGF-like factors, etc. Davis et al. use the fusion protein as a pharmaceutical composition wherein the targeted enzyme is protease and use the pharmaceutical composition for autoimmune disease, infectious diseases , cancer, etc. Davis et al. chimeric protein is chemically cross-linked fusion protein not a fusion protein made by cotranslation of respective genes. Protein conjugates can be made either by chemical conjugation or by gene fusion methods but gene fusion methods have some particular advantages (see last paragraph of column one of page 571 of Bhatia et al Intl. J. Cancer 2000, 85, 571-577)

It is well known in the prior art how to make fusion protein by translation of a chimeric gene fusion (such as references supplied in the amendment by the applicants and also Bhatia et al Intl. J. Cancer 2000, 85, 571-577). Bhatia et al teach antibody-targeted enzymes made by gene fusion method. Therefore, one knowledgeable in prior art is **motivated** to make the protein conjugate of Davis et al by gene fusion methodology as taught by Bhatia et al.

Whitcomb et al. (US PAT4510251) teach mesotrypsin – a trypsin-like protease (page 10 1st paragraph) that is fairly stable to proteolytic cleavage and also teach that mesotrypsin rapidly degrades and inactivates zymogens and other polypeptides.

As such it would have been obvious to one of ordinary skill in the art to use mesotrypsin – a trypsin-like protease that is fairly stable to proteolytic cleavage as

taught by Whitcomb et al. and make the fusion protein of Davis et al. by the method Bhatia et al. and use the resulting adzyme to inactivate substrate polypeptides by catalyzing the proteolytic cleavage of the said substrate polypeptide.

Claims 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al. (WO 00/64485), in view of Bhatia et al (Intl. J. Cancer 2000, 85, 571-57) and Whitcomb et al. (US PAT 6406846) as applied to claims 1, 4-5, 14, 18 19-21, 22-27, 30 -34, 37-38, 41 above, and further in view of Guo et al. (Biotech. and Bioeng. 2000, 70, 456-463).

Davis et al. teach fusion proteins wherein enzymes (serine protease, chymotrypsin, etc) which catalyze degradation of a specific target are conjugated to binding partners wherein the binding partner is an antibody (immunoglobulin) through **a linker but not** through Gly_4Ser type of linker. Bhattia et al. and Whitcomb et al. are described above.

Guo et al. teach fusion proteins wherein enzyme (ASNase) conjugated to immunoglobulin or fragment or antibody (scFV) by a linker polypeptide $(Gly_4Ser)_3$.

As such it would have been obvious to one of ordinary skill in the art to use mesotrypsin – a trypsin-like protease that is fairly stable to proteolytic cleavage as taught by Whitcomb et al. to make a fusion protein as taught by Davis et al. by the method Bhatia et al conjugated via a linker as taught by Guo et al. and use the resulting adzyme to inactivate substrate polypeptides by catalyzing the proteolytic cleavage of the said substrate polypeptide.

Applicants' argument against combining Davis et al. and Whitcomb et al is not found persuasive. Applicants' argue that Davis et al. chimeric protein is chemically cross-linked protein conjugate and is not made by cotranslation of respective gene is true; however, applicants' specification, as well as prior art (Bhatia et al Intl. J. Cancer 2000, 85, 571-577) teach that fusion protein can be made in a variety of ways, including chemical coupling and cotranslation using recombinant nucleic acid. Each method (chemical coupling or cotranslation using recombinant nucleic acid) of making fusion protein (chimeric protein) has its advantages and disadvantages. Davis et al state some advantages of making chimeric protein (fusion protein) by chemical coupling. However; it is well known in the prior art how to make fusion protein by chimeric gene (such as references supplied in the amendment by the applicants and also Bhatia et al Intl. J. Cancer 2000, 85, 571-577). There is **an advantage** (Bhatia et al Intl. J. Cancer 2000, 85, 571-577, page 571, 3rd paragraph) to make fusion protein by gene fusion method because it is easier and there is more control on coupling (N-terminal fusion to C-terminal) two genes and gives pure product compare to chemical conjugation. Thus one knowledgeable in prior art is **motivated** to make protein conjugate of Davis et al by gene fusion methodology (as taught by Bhatia et al). Applicants argument that Davis fusion protein can not be modified by introducing $(Gly_4\ Ser)_3$ as taught by Guo et al, is not found persuasive because the rejection does not suggest using the linker of Guo et al. in constructing a chemical conjugate as taught by Davis et al. but instead suggests using the linker of Guo et al. in constructing a fusion protein made by the method of Bhattia et al. Davis et al itself teach to introduce linker group in between catalytic

domain and targeting domain and Guo et al, taught how to produce a protein (ASNase) conjugated to immunoglobulin (scFV) by a linker polypeptide $(Gly_4Ser)_3$. One knowledgeable in prior art can make a fusion protein by using chimeric gene comprising mesotrypsin domain, linker group and targeting domain.

Applicants augment against Sallberg in 103 rejection is moot as the rejection using Sallberg et al is withdrawn.

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Double Patenting Rejection

Rejection of claims 1, 4-5, 14-27, and 30-34, 37-41 as provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4-25, and 30-41 of copending Application No.10792498 is maintained.

Rejection of claims 1, 4-5, 14-27, and 30-34, 37-41 as provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4-38, 40-46, 52-60, 66-104, 107-134 of copending Application No.10,650592 is maintained.

Examiner agrees with applicant that the provisional Double patenting rejections may be withdrawn when all claims are otherwise allowable if the copending application is not allowed (however see MPEP 804 I(B)(1) for situations where this may not be the case or when applicant submit terminal disclaimer, however until one of these conditions apply the rejections will be maintained.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat T. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-272-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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